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A Convenient Synthesis of Furanose-Free D-Fucose Per-*O*-Acetates and a Precursor for Anthrose

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Methyl 3,4-*O*-isopropylidene-α- or β-D-galactopyranoside was iodinated with triiodoimidazole in the presence of triphenylphosphane and the corresponding 6-deoxy-6-iodo derivatives **5** or **6**, respectively, were converted to furanose-free 1,2,3,4-tetra-*O*-acetyl-α,β-D-fucopyranose. A key intermediate for chemical synthesis of anthrose, a constituent of the tetrasaccharide of major glycoprotein of *Bacillus anthracis* exosporium, 1-*O*-acetyl-4-azido-2-*O*-benzoyl-3-*O*-benzyl-4,6-dideoxy-α,β-D-glucopyranose, was synthesized from **5** or **6** in 7 steps. The latter was readily converted into the corresponding 1-*O*-trichloroacetimidate.

Introduction

Both D- and L-fucose occur in nature[1] but, commercially, the D-enantiomer is much more expensive than its L-counterpart. Several syntheses of D-fucose have been described, all based on deoxygenation at the 6-position of various derivatives of D-galactose. The most convenient syntheses of D-fucose are that of Schmidt[2] and its more recent variation by Lerner,[3] which are based on further conversion of the product of deoxygenation at C-6 in 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.

Per-*O*-acetates of D- and L-fucopyranose are essential starting materials for making a variety of complex carbohydrate derivatives. Unfortunately, acetylation of fucose, either with NaOAc/Ac_2O[4] or pyridine/Ac_2O reagent[3,5] affords a mixture of pyranose and furanose acetates. When such mixtures are used as a starting material (e.g. ref.[6–8]) purification of products of further conversion may be difficult.

Anthrose [= 4,6-dideoxy-4-(3-hydroxy-3-methylbutyramido)-2-methyl-D-glucopyranose, see Figure 1], is the upstream terminal moiety of the tetrasaccharide side chain of the major glycoprotein of *Bacillus anthracis* exosporium.[9] The original synthesis[10] of the rare sugar and a glycosyl donor[11] for its precursor started with methyl α-D-mannopyranoside. Shorter syntheses of anthrose precursors have been published.[7,12] More recently, Crich et al.[13] and Doherty et al.[14] synthesized other anthrose precursors. Here we describe convenient preparation of furanose free 1,2,3,4-tetra-*O*-α,β-D-fucopyranose and a glycosyl donor for an anthrose precursor from the commercially available methyl α- or β-D-galactopyranoside.

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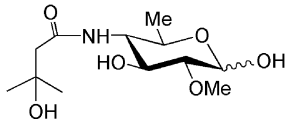


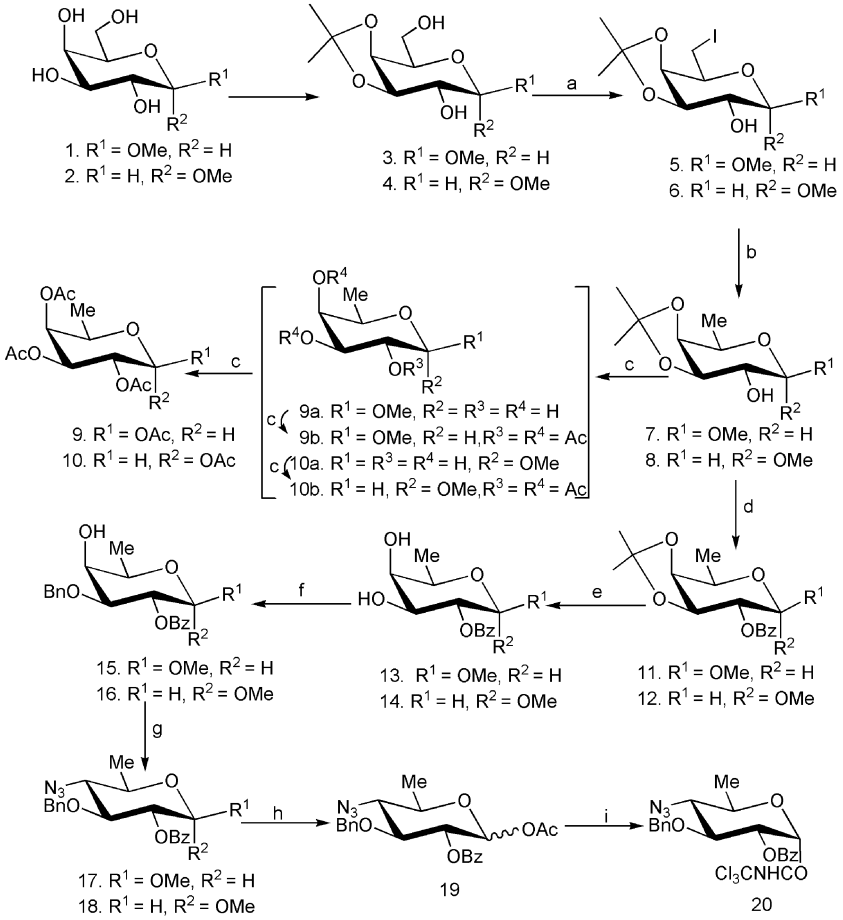
Figure 1. Structure of anthrose.

Results and Discussion

In their very carefully executed work, Leaback et al.[15] showed convincingly that the product of acetylation of fucose with the pyridine/Ac_2O reagent contains furanoses, even when the reaction is conducted at 0 °C. Their results are in full agreement with our own findings.[4] Furannose structures are also present among poducts of acetylation of fucose with NaOAc/Ac_2O reagent[4] or acetylation under acidic conditions.[15] Clearly, recent claims in the literature that acetylation of fucose with the Ac_2O/pyridine reagent afforded quantitative[7] or 98% yield of furanose-free mixtures of per-*O*-acetates,[8] or only the β-anomer (94%)[16] are unrealistic. Similarly, the possibility of formation of furanosides during acid-catalyzed alcoholysis of 1,2:3,4-di-*O*-isopropylidene-α-D-fucopyranose is often ignored, and the proof of absence of furanosides in the product of such reaction is not provided (for example ref.[17]). Crystalline 1,2,3,4-tetra-*O*-acetyl-α-D-fucopyranose has been isolated[3,5] in up to 75% yield from products of acetolysis of its most readily available synthetic intermediate, 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.[3,5,18]
Pure 1,2,3,4-tetra-*O*-acetyl-β-D-fucopyranose has not been described previously. Essential to obtaining the title compounds conveniently and in high yield is ready access to a fucose derivative from which furanose structures can not be formed under acetolysis conditions. Such intermediates are,

for example, methyl 2,3,4-tri-*O*-acetyl-α-[19,20] or β-D-fucopyranoside.[21,22] We can now generate these compounds very efficiently, which makes the title acetates readily available.

Rather than making 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose the starting point of our approach, we used the commercially available methyl α- (**1**) or β-D-galactopyranoside (**2**). (Scheme 1). Glycosides **1** and **2** were first converted[23] to the corresponding 3,4-*O*-isopropylidene derivatives **3** and **4**, respectively. Subsequent deoxygenation at C-6 was effected by iodination, which was previously performed by many investigators. Methyl 6-deoxy-6-iodo-3,4-*O*-isopropylidene-α-D-galactopyranoside (**6**) was first obtained by Schmidt and Wernicke[24] who treated methyl 3,4-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranoside with NaI. According to the more recent reports,[25–27] direct iodination of diol **4** or its β-anomer **3** with iodine in the presence of imidazole gave the corresponding 6-iodo derivatives in yields up to 73%.[27] When we effected that conversion at optimized conditions we found it a one-product reaction, and obtained the desired 6-iodo derivatives **5** and **6** in 78 and 95% yield, respectively. The minimal losses encountered during work-up and isolation were manipulative. Subsequent hydrogenolysis gave fucose derivatives **7** and **8** in virtually theoretical yield. All products in the sequence described were fully characterized. Conversion of each of **7** and **8** to the title acetates **9** and **10**, namely hydrolysis of the *O*-isopropylidene group and acetylation/acetolysis, could be performed as a one-pot transformation. The isopropylidene group in **7** or **8** was first removed by AcOH-catalyzed hydrolysis, followed by H_2SO_4-catalyzed acetylation. The amount of H_2SO_4 was kept low during the latter transformation, to avoid acetolysis of the glycoside before the acetylation would be complete, lest acetolysis of HO-4-free compound might lead to formation of furanose structures. The acetolysis was then effected by increasing the concentration of H_2SO_4. The TLC and NMR spectra of the mixture of **9** and **10** did not reveal presence of furanoses. Thus, the crude product of acetolysis performed in this way can be used for further conversions when the absence of furanose structures is important but anomeric purity of the starting material is not. The two anomeric acetates could, however, be separated by chromatography, which allowed isolation and full characterization of the hitherto unknown β-acetate **9**. The original mode of preparation and more negative value of $[\alpha]_D$ found for **9**, as compared to that reported,[5] indicates that the material described previously contained some α anomer.



Scheme 1. Reagents and conditions: a. TPP, imidazole, I_2, toluene, 110 °C; b. Pd/C, MeOH, H_2; c. (1) 80% HOAc, 70 °C; (2) Ac_2O, Ac_2O/HOAc/H_2SO_4; d. BzCl, pyridine; e. TFA, CH_2Cl_2; f. Bu_2SnO, Bu_4NI, BnBr, toluene; g. (1) MsCl, pyridine/CH_2Cl_2. (2). NaN_3, 15-crown-5 ether, DMF; h. Ac_2O/HOAc/H_2SO_4; i. (1) hydrazine acetate, DMF. (2) DBU, CCl_3CN, CH_2Cl_2.

The tetrasaccharide side chain of the major glycoprotein of *Bacillus anthracis* exosporium is an important biomarker for detection of *Bacillus anthracis* spores[28] and, possibly, a key antigenic component of a future conjugate vaccine for anthrax.[7,11,12] A prerequisite for making life science tools involving the synthetic tetrasaccharide is ready access to anthrose, whose synthesis often starts from fucose peracetate. With the intermediate **7** or **8** in hand, we used each of them separately to prepare the same glycosyl donor for the latent anthrose, the glycosyl imidate **20**. Benzoylation at O-2 followed by selective hydrolysis, to remove the 3,4-*O*-isopropylidene group, afforded the 2-*O*-benzoyl-D-fucopyranosides **13** or **14**. Selective 3-*O*-benzylation via stannylation (→**15/16**) was followed by mesylation (→**17/18**), and treatment of the mesyl derivatives thus formed with NaN_3 furnished glycosides **17** or **18**, which were acetolyzed (→**19**). The ratio of anomeric acetates (α/β = 5–6:1) in **19** was independent of the configuration of the starting glycoside. Acetates **19** were converted into the anomerically pure (TLC, NMR) α-trichloroacetimidate **20** by successive treatment with hydrazine acetate and CCl_3CN.

Experimental Section

General Methods: Optical rotations were measured at ambient temperature with a Perkin–Elmer automatic polarimer, Model 341. All reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 or C18 RP silica-gel-coated glass slides. Column chromatography was performed by elution from columns of silica gel with CombiFlash Companion Chromatograph (Isco Inc.). Solvent mixture less polar than those used for TLC were used at the onset of separation. NMR spectra were measured at 300 MHz (^{1}H) and 75 MHz (^{13}C) with a Varian Gemini or Varian Mercury spectrometers, or at 600 MHz (^{1}H) and 150 MHz (^{13}C) with a Bruker Avance 600 spectrometer. Assignments of NMR signals were made by homonuclear and heteronuclear 2-dimensional correlation spectroscopy, run with the software supplied with the spectrometers. Liquid Chromatography-Electron Spray-Ionization Mass Spectrometry (ESI-MS) was performed with a Hewlett–Packard 1100 MSD spectrometer. Attempts have been made to obtain correct combustion analysis data for all new compounds. However, some compounds tenaciously retained traces of solvents, despite exhaustive drying, and analytical %C values could not be obtained within ±0.4%. Structures of these compounds follow unequivocally from the mode of synthesis and NMR and MS data. Solutions in organic solvents were dried with anhydrous Na_2SO_4, and concentrated at 40 °C/2 kPa.

Methyl 3,4-Isopropylidene-β-D-galactopyranoside (3) and Methyl 3,4-Isopropylidene-α-D-galactopyranoside (4): These compounds were prepared as described[23] **3**: M.p. 137–138 °C (from EtOAc; ref.[11] 134–135 °C). **4**: M.p. 104–105 °C (from EtOAc; ref.[12] 103–104 °C).

Methyl 6-Deoxy-6-iodo-3,4-isopropylidene-β-D-galactopyranoside (5): The solvent (ca. 100 mL) was distilled off at atmospheric pressure from a solution of methyl 3,4-isopropylidene-β-D-galactopyranoside (**3**)[23] (21.8 g, 93.2 mmol) in toluene (300 mL). The solution was cooled to ca. 60–70 °C, then TPP (35.1 g, 134 mmol), imidazole (20.7 g, 304 mmol), and iodine (31.2 g, 123 mmol) were quickly added. The mixture was stirred at 110° for 1.5 h, when TLC (1:1 hexane/EtOAc) showed that the starting material was consumed. A solution of $NaHCO_3$ (32 g) in H_2O (100 mL) was added slowly with stirring, followed by a small amount of iodine until persistent color developed. 10% aqueous sodium thiosulfate was added dropwise and, when the mixture became colorless, the mixture was diluted with EtOAc, washed with brine, dried, concentrated and chromatography (hexane/EtOAc, 3:1) gave **5** (24.8 g, 78%). M.p. 117–118 °C (from EtOAc; ref.[25] 122 °C). $[\alpha]_D$ = +22 [*c* = 0.9, $CHCl_3$; ref.[25] $[\alpha]_D$ = +31 (*c* = 1.1, $CHCl_3$)]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.31 (dd, $J_{3,4}$ = 5.4, $J_{4,5}$ = 2.2 Hz, 1 H, 4-H), 2.56–2.45 (m, $J_{1,2}$ = 8.3, $J_{2,3}$ = 7.3, $J_{3,4}$ = 5.4 Hz, 2 H, 1-H, 3-H), 3.92 (m, 1 H, 5-H), 3.58 (s, 3 H, OCH_3), 3.54 (m, 1 H, 2-H), 3.45–3.40 (m, 2 H, 6-H), 2.47 (br. s, 1 H, 2-OH), 1.51 and 1.36 (2 s, each 3 H, 2 CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 110.2 (C_q), 103.1 (C-1), 78.6 (C-3), 73.8 (C-4), 73.7 (C-5), 73.4 (C-2), 57.0 (OCH_3), 28.0 (CH_3), 26.2 (CH_3), 1.6 (C-6) ppm. $C_{10}H_{17}IO_5$ (344.14): calcd. C 34.90, H 4.98; found C 35.09, H 5.02.

Methyl 6-Deoxy-6-iodo-3,4-isopropylidene-α-D-galactopyranoside (6): Treatment of methyl 3,4-isopropylidene-α-D-galactopyranoside (**4**)[23] as described for **3** gave **6** (95%). M.p. 87–88 °C (from EtOH; ref.[27] 84–86 °C). $[\alpha]_D$ = +113 [*c* = 1.0, $CHCl_3$; ref.[27] $[\alpha]_D$ = +118 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.77 (d, $J_{1,2}$ = 4.0 Hz, 1 H, 1-H), 4.32 (dd, $J_{3,4}$ = 2.2, $J_{4,5}$ = 6.3 Hz, 1 H, 4-H), 4.29 (t, *J* = 5.9 Hz, 1 H, 3-H), 4.13 (m, 1 H, 5-H), 3.86 (m, $J_{1,2}$ = 4.1 Hz, 1 H, 2-H), 3.51 (s, 3 H, OCH_3), 3.35–3.29 (m, 2 H, 6-H), 2.52 (d, *J* = 5.4 Hz, 1 H, 2-OH), 1.49 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 109.7 (C_q), 98.2 (C-1), 75.7 (C-3), 73.4 (C-4), 69.3 (C-5), 68.5 (C-2), 55.5 (OCH_3), 27.3 (CH_3), 25.6 (CH_3), 2.76 (C-6) ppm. $C_{10}H_{17}IO_5$ (344.14): calcd. C 34.90, H 4.98; found C 34.79, H 4.96.

Methyl 3,4-Isopropylidene-β-D-fucopyranoside (7): Hydrogenolysis of **5** (6.5 g, 18.8 mmol) over Pd/C (1.3 g), in the presence of Et_3N (4.0 g, 37.7 mmol) using methanol (55 mL) as solvent gave, after chromatography, **7** (3.9 g, 95%). M.p. 67–69 °C (from EtOAc). $[\alpha]_D$ = +22.9 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.05 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1-H), 4.04 (dd, $J_{2,3}$ = 7.3, $J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 4.00 (dd, $J_{4,5}$ = 2.2, $J_{3,4}$ = 5.5 Hz, 1 H, 4-H), 3.86 (m, 1 H, 5-H), 3.55–3.50 (m, 4 H, OCH_3 and 2-H), 2.52 (d, *J* = 2.2 Hz, 1 H, 2-OH), 1.53 and 1.35 (2 s, each 3 H, 2 CH_3), 1.42 (d, $J_{5,6}$ = 6.6 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 109.8 (C_q), 103.1 (C-1), 78.7 (C-3), 76.2 (C-4), 73.6 (C-2), 69.1 (C-5), 56.8 (OCH_3), 23.1 and 26.6 (2 CH_3), 16.4 (C-6). $C_{10}H_{18}O_5$ (231.6) +0.75H_2O: calcd. C 51.82, H 8.48; found C 51.67, H 8.48.

Methyl 3,4-Isopropylidene-α-D-fucopyranoside (8): Treatment of **6** as described for **5** gave amorphous **8** (94%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.71 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1-H), 4.19 (t, *J* = 6.7 Hz, 1 H, 3-H), 4.12–4.08 (m, 1 H, 5-H), 4.05 (dd, $J_{3,4}$ = 2.4, $J_{4,5}$ = 6.0 Hz, 1 H, 4-H), 3.78 (br. s, 1 H, 2-H), 3.43 (s, 3 H, OCH_3), 2.63 (br. s, 1 H, 2-OH), 1.51 and 1.35 (2 s, each 3 H, 2 CH_3), 1.32 (d, $J_{5,6}$ = 6.7 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 109.0 (C_q), 98.6 (C-1), 76.1 (C-3), 75.6 (C-4), 69.4 (C-2), 63.5 (C-5), 55.3 (OCH_3), 27.7 (CH_3), 25.8 (CH_3), 16.1 (C-6) ppm. ES-TOF-MS (pos. ion.): *m*/*z* = 266.1 [M + Li+CH_3CN]$^+$. The compound was fully characterized as the corresponding 2-*O*-benzoyl derivative **12**, described below.

1,2,3,4-Tetra-*O*-acetyl-α-D-fucopyranoside (10) and 1,2,3,4-Tetra-*O*-acetyl-β-D-fucopyranoside (9): A solution of **7** (700 mg, 3.2 mmol) in 80% aqueous HOAc (5 mL) was stirred at 70 °C for 1.5 h, when TLC (1:1 hexane/acetone) showed that the starting material was consumed and that one slower moving product was formed. The mixture was cooled to room temperature and the solvent was evaporated. The residue was dissolved in acetic anhydride (10 mL), Ac_2O/HOAc/H_2SO_4 (10:4:0.1, 0.1 mL) was added, and the mixture

was stirred at ambient temperature for 1 h, when TLC (3:2 hexane/acetone) indicated that the desired 2,3,4-tri-*O*-acetyl derivative was formed. The reaction was cooled to 0 °C, a mixture of Ac_2O/HOAc/H_2SO_4 (10:4:0.1, 1.0 mL) was added with stirring, the cooling was removed, and the mixture was stirred for 45 min, when TLC (RP, 1:1 acetone/water) showed that two slightly slower moving products were formed. NaOAc trihydrate (10 mg) was added, to neutralize H_2SO_4, the mixture was concentrated, and the residue was partitioned between EtOAc and a mixture of aqueous $NaHCO_3$ and brine. Concentration of organic phase gave a mixture of title acetates. Chromatography (9:1 hexane/acetone) gave first **10** (850 mg, 80%). M.p. 93–94 °C (from EtOAc) (ref.[5] 93 °C), $[\alpha]_D$ = +120 (*c* = 1.1, $CHCl_3$); [ref.[5] $[\alpha]_D$ = +122 (*c* = 1, $CHCl_3$)]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.33 (d, $J_{1,2}$ = 3.3 Hz, 1 H, 1-H), 5.36–5.30 (m, 3 H, 2-H, 3-H and 4-H), 4.29–4.28 (m, 1 H, 5-H), 2.18, 2.15, 2.02, 2.00 (4 s, each 3 H, 4 $COCH_3$), 1.16 (d, $J_{5,6}$ = 6.5 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3, 169.9, 169.7, 168.9, 89.7 (C-1), 70.3, 67.6, 67.0 (C-5), 66.3, 20.7, 20.4 (2 C), 20.3, 15.7 (C-6) ppm. $C_{14}H_{20}O_9$ (332.30): calcd. C 50.60, H 6.07; found C 50.93, H 6.37.

Eluted next was the amorphous compound **9** (143 mg, 13%). $[\alpha]_D^{25}$ = +32 [*c* = 2.1, $CHCl_3$; ref.[5] +47 (*c* = 2.1, $CHCl_3$)]. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.68 (d, $J_{1,2}$ = 8.4 Hz, 1 H, 1-H), 5.32 (t, *J* = 9.8 Hz, 1 H, 2-H), 5.27 (d, $J_{3,4}$ = 3.4 Hz, 1 H, 4-H), 5.08 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.5 Hz, 1 H, 4-H), 3.97 (q, *J* = 6.4, *J* = 12.9 Hz, 1 H, 5-H), 2.19, 2.12, 2.04, 2.00 (4 s, each 3 H, $COCH_3$), 1.22 (d, $J_{5,6}$ = 6.4 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.5, 170.0, 169.4, 169.1, 92.0 (C-1), 71.8 (C-3), 70.1 (C-5), 69.8 (C-4), 67.8 (C-2), 20.8, 20.6 (2 C), 20.5, 15.8 (C-6) ppm. $C_{14}H_{20}O_9$ (332.30): calcd. C 50.60, H 6.07; found C 50.76, H 6.24.

Methyl 2-*O*-Benzoyl-3,4-isopropylidene-β-D-fucopyranoside (11): Benzoyl chloride (0.3 mL, 2.19 mmol) was added to a solution of **7** (320 mg, 1.46 mmol) in pyridine (4 mL), and the reaction was quenched after 1 h by addition of MeOH (2 mL). The mixture was concentrated, the residue was partitioned between EtOAc and brine, dried, and concentrated. Chromatography (5:1 hexane/EtOAc) gave **11** (440 mg, 94%). M.p. 105–107 °C (from EtOH). $[\alpha]_D$ = +56 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18–7.50 (m, 5 H, aromatic H), 5.22 (t, *J* = 8.0 Hz, 1 H, 2-H), 4.37 (d, $J_{1,2}$ = 8.0 Hz, 1 H, 1-H), 4.31 (dd, $J_{2,3}$ = 7.4, $J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 4.08 (dd, $J_{3,4}$ = 5.5, $J_{4,5}$ = 2.2 Hz, 1 H, 4-H), 3.94 (m, 1 H, 5-H), 3.46 (s, 3 H, OCH_3), 1.62 and 1.35 (2 s, each 3 H, 2 CH_3), 1.46 (d, $J_{5,6}$ = 6.6 Hz, 3 H, H-6) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.67 (CO), 133.1, 130.2, 130.0, 128.4, 110.4 (C_q), 101.5 (C-1), 77.48 (C-3), 76.7 (C-4), 73.8 (C-2), 69.2 (C-5), 56.7 (OCH_3), 28.0, 26.5 (2 CH_3), 16.7 (C-6) ppm. $C_{17}H_{22}O_6$ (322.35): calcd. C 63.34, H 6.88; found C 63.37, H 6.88.

Methyl 2-*O*-Benzoyl-3,4-isopropylidene-α-D-fucopyranoside (12): Compound **12** was synthesized (97%) as described for the β anomer. M.p. 60–62 °C (from EtOH). $[\alpha]_D$ = +184 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.13 (dd, $J_{1,2}$ = 3.5, $J_{2,3}$ = 8.2 Hz, 1 H, 2-H), 4.92 (d, $J_{1,2}$ = 3.5 Hz, 1 H, 1-H), 4.48 (dd, $J_{2,3}$ = 8.2, $J_{3,4}$ = 5.2 Hz, 1 H, 3-H), 4.17–4.13 (m, 2 H, 4-H and 5-H), 3.37 (s, 3H, OCH_3), 1.56 (s, 3 H, CH_3), 1.42 (d, $J_{5,6}$ = 6.3 Hz, 3 H, 6-H), 1.36 (s, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.0 (CO), 133.3, 130.1, 129.9, 128.5, 109.6 (C_q), 97.5 (C-1), 76.4 (C-4), 73.7 (C-3), 72.7 (C-2), 63.2 (C-5), 55.7 (OCH_3), 28.2 (CH_3), 26.6 (CH_3), 16.1 (C-6) ppm. ES-TOF-MS (pos. ion.): *m*/*z* = 370.1 [M + Li + AcN]$^+$. $C_{17}H_{22}O_6$ (322.35): calcd. C 63.34, H 6.88; found C 63.60, H 6.86.

Methyl 2-*O*-Benzoyl-β-D-fucopyranoside (13): A solution of **11** (210 mg, 0.65 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (0.7 mL) at room temperature for 1 h. The mixture was concentrated, and the residue was chromatographed (10:1 CH_2Cl_2/acetone:) to give the title compound **13** (178 mg, 97%). M.p. 140–142 °C (from EtOH). $[\alpha]_D$ = –13.8 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.02–7.40 (m, 5 H, aromatic H), 5.17 (dd, $J_{1,2}$ = 8.0, $J_{2,3}$ = 9.2 Hz, 1 H, 2-H), 4.16 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 3.80–3.77 (m, 2 H, 3-H and 4-H), 3.67 (dd, $J_{5,6}$ = 6.6 Hz, 1 H, H-5), 3.58 (d, *J* = 7.5 Hz, 1 H, OH), 3.48 (s, 3 H, OCH_3), 3.12 (d, *J* = 6.7 Hz, 1 H, OH), 1.37 (d, $J_{5,6}$ = 6.6 Hz, 3 H, H-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.9 (CO), 133.1, 129.8, 129.7, 128.2, 101.7 (C-1), 73.7 (C-2), 73.0 (C-4), 71.8 (C-3), 70.5 (C-5), 56.6 (OCH_3), 16.1 (C-6) ppm. $C_{14}H_{18}O_6$ (282.29): calcd. C 59.57, H 6.43; found C 59.38, H 6.58.

Methyl 2-*O*-Benzoyl-α-D-fucopyranoside (14): Treatment of **12** as described for **11** gave **14** (95%). M.p. 168–170 °C (from EtOH). $[\alpha]_D$ = +156 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.20 (dd, $J_{1,2}$ = 3.9, $J_{2,3}$ = 10.2 Hz, 1 H, 2-H), 4.98 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1-H), 4.16 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 4.06–4.04 (m, 1 H, 5-H), 3.87 (d, *J* = 2.7 Hz,1 H, 4-H), 3.39 (s, 3 H, OCH_3), 1.34 (d, $J_{5,6}$ = 6.6 Hz, 3H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.0, 133.3, 129.9, 129.5, 128.3, 97.4 (C-1), 72.3 (2 C, C-2, C-4), 68.8 (C-3). 65.2 (C-5), 55.4 (OCH_3), 16.0 (C-6) ppm. ES-TOF-MS (pos. ion.): *m*/*z* = 420.1 [M + Li + AcN]$^+$, 379.1 [M + Li]$^+$. $C_{14}H_{18}O_6$ (282.29): calcd. C 59.57, H 6.43; found C 59.86, H 6.62.

Methyl 2-*O*-Benzoyl-3-*O*-benzyl-β-D-fucopyranoside (15): The solvent (40 mL) was removed from a mixture of **13** (3.1 g, 11 mmol) and Bu_2SnO (2.72 g, 11 mmol) in toluene (80 mL) which had been heated under reflux for 1 h. After cooling to 60 °C, Bu_4NI (811 mg, 2.19 mmol) and BnBr (1.7 mL, 14.3 mmol) was added, and the mixture was stirred at 110 °C for 3.5 h. After concentration, the residue was chromatographed (hexane/acetone, 9:1) to give the amorphous compound **15** (3.1 g, 74%). $[\alpha]_D$ = +48 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.03–7.14 (m, 10 H, aromatic H), 5.43 (dd, $J_{1,2}$ = 8.8, $J_{2,3}$ = 9.8 Hz, 1 H, 2-H), 4.68–4.51 (ABq, *J* = 12.3 Hz, 2 H, $ArCH_2$), 4.39 (d, $J_{1,2}$ = 8.0 Hz, 1 H, 1-H), 3.88 (dd, $J_{2,4}$ = 3.4, $J_{4,5}$ = 1.1 Hz, 1 H, 4-H), 3.64 (dd, $J_{2,3}$ = 9.7, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 3.62–3.61 (m, 1 H, 5-H), 3.45 (s, 3 H, OCH_3), 1.42 (d, $J_{5,6}$ = 2.5 Hz, 3 H, H-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.3 (CO), 137.0, 132.9, 129.9, 129.7, 128.2, 127.8, 127.7, 101.7 (C-1), 78.4 (C-3), 71.1 ($ArCH_2$), 70.9 (C-2), 70.2 (C-5), 68.6 (C-4), 56.3 (OCH_3), 16.2 (C-6) ppm. ES-TOF-MS (pos. ion.): *m*/*z* = 395.1471 ([M + Na]$^+$; calcd. 395.1476). $C_{21}H_{24}O_6$ (372.41): calcd. C 67.73, H 6.50; found C 67.78, H 6.70.

Methyl 2-*O*-Benzoyl-3-*O*-benzyl-α-D-fucopyranoside (16): Treatment of **14**, as described for **13**, gave amorphous **16** (83%). $[\alpha]_D$ = +155 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.38 (dd, $J_{1,2}$ = 3.8, $J_{2,3}$ = 10.2 Hz, 1 H, 2-H), 5.01 (d, $J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 4.69 (AB_q, *J* = 12 Hz, 2 H, $ArCH_2$), 4.03 (dd, $J_{3,4}$ = 3.3, $J_{2,3}$ = 10.1 Hz, 1 H, 3-H), 3.98–3.94 (m, 1 H, 5-H), 3.92 (dd, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.2 Hz, 1 H, 4-H), 3.35 (s, 3 H, OCH_3), 1.34 (d, $J_{5,6}$ = 6.6 Hz, 3 H, H-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.0, 137.6, 133.1, 129.9, 129.8, 128.4, 127.9, 127.7, 97.4 (C-1), 75.4 (C-3), 72.0 ($ArCH_2$), 70.6 (C-2), 69.8 (C-4), 65.1 (C-5), 55.3 (OCH_3), 16.1 (C-6). ES-TOF-MS (pos. ion.): *m*/*z* = 395.1[M + Na]$^+$. $C_{21}H_{24}O_6$ (372.41): calcd. C 67.73, H 6.50; found C 67.86, H 6.61.

Methyl 4-Azido-2-*O*-benzoyl-3-*O*-benzyl-4,6-dideoxy-β-D-glucopyranoside (17): MsCl (4.2 mL, 50 mmol) was added at 0 °C to a stirred solution of **15** (3.0 g, 8.0 mmol) in CH_2Cl_2 (15 mL) and pyridine (5 mL). The cooling was removed, and the mixture was stirred overnight. Aqueous $NaHCO_3$ was added slowly, and when effervescence ceased, the mixture was diluted with CH_2Cl_2, washed with

brine, the organic phase was dried, concentrated, and chromatography (hexane/EtOAc, 4:1) gave methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-mesyl-β-D-fucopyranoside (3.5 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.41 (dd, $J_{1,2}$ = 7.9, $J_{2,3}$ = 10.2 Hz, 1 H, 2-H), 5.05 (dd, $J_{3,4}$ = 3.1, $J_{4,5}$ = 0.6 Hz, 1 H, 4-H), 4.74–4.50 (ABq, J = 11.7 Hz, 2 H, $ArCH_2$), 3.78 (m, 1 H, 5-H), 3.74 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.1 Hz, 1 H, 3-H), 3.47 (s, 3 H, OCH_3), 3.12 (s, 3 H, OMs), 1.45 (d, $J_{5,6}$ = 6.6 Hz, 3 H, 6-H). ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.2 (CO), 136.4, 133.1, 129.7, 129.6, 128.3 (3 C), 128.0 (2 C), 101.7 (C-1), 80.2 (C-4), 77.0 (C-3), 72.1 ($ArCH_2$), 70.2 (C-2), 69.1 (C-5), 56.6 (OCH_3), 39.1 (OMs), 16.6 (C-6) ppm.

A solution of the above product (2.9 g, 6.4 mmol) in DMF(15 mL) was treated at 120 °C with NaN_3 (1.5 g, 23 mmol) and 15-crown-5 ether (500 mg, 2.2 mmol) for 4 h. After concentration, the residue was chromatographed (hexane/EtOAc, 5:1) to give compound **17** (2.32 g, 91%). M.p. 76–77 °C (from EtOH). $[\alpha]_D$ = +166 (c = 1.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.25 (dd, $J_{1,2}$ = 8.0, $J_{2,3}$ = 9.5 Hz, 1 H, 2-H), 4.74–4.63 (ABq, J = 10.8 Hz, 2 H, $ArCH_2$), 4.39 (d, $J_{1,2}$ = 8.8 Hz, 1 H, 1-H), 3.69 (t, J = 9.3 Hz, 1 H, 3-H), 3.44 (s, 3 H, OCH_3), 3.36–3.28 (m, 2 H, 4-H and 5-H), 1.41 (d, $J_{5,6}$ = 6.6 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.0 (CO), 137.0, 133.2, 129.8, 129.7, 128.2 (2 C), 127.8, 101.7 (C-1), 81.2(C-3), 74.9 ($ArCH_2$), 73.7 (C-2), 70.8 (C-5), 67.6 (C-4), 56.7 (OCH_3), 18.3 (C-6) ppm. $C_{21}H_{23}N_3O_5$ (397.42): calcd. C 63.46, H 5.83; found C 63.36, H 5.77.

Methyl 4-Azido-2-*O*-benzoyl-3-*O*-benzyl-4,6-dideoxy-α-D-glucopyranoside (18): Compound **16** (2.2 g, 5.9 mmol) was treated as described for **15**, to give after chromatography, syrupy methyl 2-*O*-benzoyl-3-*O*-benzyl-4-*O*-mesyl-α-D-glucopyranoside (2.54 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.35 (dd, $J_{1,2}$ = 3.8, $J_{2,3}$ = 10.8 Hz, 1 H, 2-H), 5.08 (dd, $J_{3,4}$ = 3.2, $J_{4,5}$ = 1.3 Hz, 1 H, 4-H), 5.03 (d, $J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 4.77–4.62 (AB_q, 2 H, J = 11 Hz, $ArCH_2$), 4.15 (dd, $J_{2,3}$ = 10.6, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 4.11–4.08 (m, 1 H, 5-H), 3.37 (s, 3 H, OCH_3), 3.06 (s, 3 H, OMs), 1.37 (d, $J_{5,6}$ = 6.6 Hz, 3 H, H-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.9, 136.9, 133.3, 129.6, 128.0, 97.4 (C-1), 80.8 (C-4), 73.8 (C-3), 72.9 ($ArCH_2$), 70.3 (C-2), 64.6 (C-5), 55.5 (OCH_3), 39.1 (OMs), 16.5 (C-6) ppm. ES-TOF-MS (pos. ion.): m/z = 473.1237 ([M + Na]$^+$ calcd. 473.1246). The above product (2 g, 4.4 mmol) was treated as described for **17**, to give **18** (1.52 g, 86%). $[\alpha]_D$ = +297 (c = 1.1, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.10 (dd, $J_{1,2}$ = 3.6, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 4.96 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 4.80 (ABq, J = 10.6 Hz, 2 H, $ArCH_2$), 4.04 (t, J = 9.6 Hz, 1 H, 3-H), 3.68–3.62 (m, 1 H, 5-H), 3.49 (s, 3 H, OCH_3), 3.23 (t, J = 9.9 Hz, 1 H, 4-H), 1.33 (d, $J_{5,6}$ = 6.3 Hz, 3 H, H-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.9, 137.6, 133.5, 130.0, 129.7, 128.6, 128.5, 128.3, 97.3 (C-1), 78.3 (C-3), 75.6 ($ArCH_2$), 74.4 (C-2), 68.2 (C-4), 66.1 (C-5), 55.5 (OCH_3), 18.5 (C-6) ppm. ES-TOF-MS (pos. ion.): m/z = 445.2053 ([M + Li + CAN]$^+$, calcd. 445.2063). $C_{21}H_{23}N_3O_5$ (397.42): calcd. C 63.46, H 5.83; found C 63.38, H 5.90.

1-*O*-Acetyl-4-azido-2-*O*-benzoyl-3-*O*-benzyl-4,6-dideoxy-α,β-D-glucopyranoside (19): A solution of **17** (1.0 g, 2.5 mmol) in Ac_2O/HOAc/H_2SO_4 (14 mL, 14:4:0.1) was stirred at room temperature for 2 h. NaOAc trihydrate (300 mg) was added, and the mixture was processed as described for preparation of **9**, to give a mixture of α and β products **19** (984 mg, 92%, α/β ≈ 5:1–6:1). A similar mixture in comparable yield was obtained by treatment of **18** in the same way. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98–7.16 (m, 10 H, aromatic H), 6.35 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 5.27 (dd, $J_{1,2}$ = 3.8, $J_{2,3}$ = 9.9 Hz, 1 H. 2-H), 4.81 (ABq, J = 10.7 Hz, 2 H, $ArCH_2$), 4.01 (t, J = 9.6 Hz, 1 H, 3-H), 3.78–3.72 (m, 1 H, 5-H), 3.32 (t, J = 9.9 Hz, 1 H, 4-H), 2.12 (s, 3 H, $COCH_3$), 1.34 (d, $J_{5,6}$ = 6.3 Hz, 3 H, 6-H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 168.8, 137.1, 133.4, 130.0, 129.6, 129.1, 128.5, 128.3, 128.0,127.5, 89.5 (C-1), 78.0 (C-3), 75.4 ($ArCH_2$), 72.3 (C-2), 68.2 (C-4), 67.4 (C-5), 59.8 (OCH_3), 18.4 (C-6) ppm. ES-TOF-MS (pos. ion.): m/z = 473.2027 ([M + Li + CAN]$^+$ calcd. 473.2012). $C_{22}H_{23}N_3O_6$ (425.43): calcd. C 62.11, H 5.45; found C 61.95, H 5.47.

4-Azido-2-*O*-benzoyl-3-*O*-benzyl-4,6-dideoxy-α-D-glucopyranose 1-*O*-Trichloroacetimidate (20): Hydrazine acetate (44 mg, 0.48 mmol) was added to a stirred solution of **19** (170 mg, 0.40 mmol) in DMF (2 mL). After 2 h, the mixture was diluted with CH_2Cl_2 (35 mL) and washed with brine. The organic phase was dried and concentrated. DBU (0.03 mL, 0.2 mmol) and CCl_3CN (0.4 mL, 4 mmol) was added at 0 °C to a solution of the above, crude product in dried CH_2Cl_2 (2 mL), and the mixture was stirred for 2.5 h, when TLC (4:1 hexane/EtOAc) showed that the conversion was complete. Concentration and chromatography (8:1 hexane/EtOAc with 1% Et_3N) afforded amorphous **16** (156 mg, 74%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.5–7.0 (m, 10 H, aromatic H), 6.52 (d, $J_{1,2}$ = 3.3 Hz, 1 H, 1-H), 5.34 (dd, $J_{1,2}$ = 3.3, $J_{2,3}$ = 9.7 Hz, 1 H, 2-H), 4.80 (AB_q, J = 10.9 Hz, 2 H, $C_6H_5CH_2$), 4.14 (t, J = 9.7 Hz, 1 H, 3-H), 3.86 (m, 1 H, 5-H), 3.37 (t, J = 10.0 Hz, 1 H, 4-H), 1.39 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.3, 160.4, 137.0, 133.5, 129.7, 129.0, 128.4, 128.3, 128.2, 127.9, 93.6 (C-1), 77.5 (C-3), 75.4 ($ArCH_2$), 72.6 (C-2), 69.2 (C-5), 67.2 (C-4), 18.4 (C-6) ppm. ES-TOF-MS (pos. ion.): m/z = 67 [M + K]$^+$, 549 [M + Na]$^+$, 549.0453 ([M + Na]$^+$ calcd. 549.0475).

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